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**Global Research & Development**

14 December 2005

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**RE: Comments on Draft Guidance for Industry on Acne Vulgaris**  
**Docket No. 2005D-0340**

Dear Sir or Madam,

The following are comments on the Draft Guidance for Industry on Acne Vulgaris as published in the Federal Register on 16 September 2005. Verbiage in italics are as stated in the Draft Guidance and comments for consideration follow in regular font.

**Statistical**

- On page 10 (Line 399-Line 402), the Guidance states:

*Even if the indication is limited to only one type of lesion (i.e., either noninflammatory or inflammatory lesions of acne), as described in Section III.A., Clinical Considerations, we recommend obtaining lesion counts for both types, but only declaring one as primary in the prespecified analysis plan.*

The above paragraph suggests that when one is interested in pursuing indication for only one type of lesion, only the lesion of interest should be treated as the primary endpoint. However, on page 11 (Line 434-Line 440), the Guidance states:

*On the other hand, for an acne indication specific to a certain lesion type (see Section III.A.3., Targeted Acne Therapy), we recommend the test drug be superior to its vehicle with respect to the specified lesion type, and be noninferior to its vehicle for the other lesion type. It is important that the noninferiority margin be discussed and agreed upon with the Agency before study initiation. In addition, it is important to demonstrate superiority for success according to the IGA.*

This paragraph seems to suggest that even for an acne indication specific to a certain lesion type, one has to design the study with sufficient power for both lesion types, one

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for superiority and one for non-inferiority. Could the Agency clarify whether both lesion types need to be treated as co-primary, and if the studies need to be powered to demonstrate both statistically significant superiority for the target lesion type, and statistical noninferiority for the nontargeted lesion type? Furthermore, depending on the margin of noninferiority, the required study size may be much larger than that required to demonstrate superiority for the target lesion type.

- On page 12 (Line 511-Line 516), the Guidance states:

*It is important that the effect of dropouts be addressed in all clinical trials and analyses, and analyses be carried out to demonstrate that the study conclusions are robust with regard to handling dropouts. An approach that can be used to check robustness of study findings is the worst-case rule (assigning the best possible score to all dropouts on placebo arm and the worst score to all dropouts on the active arm and then performing an analysis including these scores).*

This is a very conservative approach. The results based on this approach may be far beyond realistic for a study with a moderate dropout rate (e.g., 10-15%) that is commonly seen in practice. A technical difficulty with this approach involves the determination of the worst possible score for lesion counts (co-primary endpoints) since the lesion counts at baseline could be very broad in range, hence, the worst (or best) case may have a different interpretation for each subject.

There is also a theoretical argument against using the worst case rule for acne studies. As part of the justification for this approach, the guidelines make the statement "It is unlikely that dropouts occur randomly, and they rarely occur completely independent of the treatment being tested..." (page 16; Line 494-Line 496). The inference is that dropouts occur differentially in the treatment groups in a manner that may favor the investigational treatment. However, many dropouts occur in acne studies with topical drugs due to local intolerance; although these are related to treatment it is hard to understand how they could bias the efficacy results obtained by a LOCF analysis in favor of the investigational treatment. In addition, if we believe that dropouts in either treatment arm may be related to lack of efficacy, then it seems illogical to assign a "best score" to any patient who drops out, whether in the placebo or active arm.

## **Clinical**

- On page 3 (Line 109-Line 110), the Guidance states:

*We recommend considering a post-treatment follow-up period to evaluate recurrences following treatment discontinuation.*

Minimum treatment duration is specified as 12 weeks. Post-treatment follow-up duration is not specified. What would the Agency suggest as post-treatment follow-up? Is this post-treatment follow-up period recommended for Phase 2 studies or pivotal Phase 3 studies?

- On page 9 (Line 350-Line 351 and Line 355-Line 357), the Guidance states:

*Photographic examples of each grade that have been agreed upon with the Agency before their use may be provided to investigators.*

Should such examples be of full face, one-side of face (e.g. 45° view), or magnified close-up photographs?

*The Agency recommends that each subject's improvement be verifiable (e.g., via photographic records of baseline and assessment time point) by Agency staff for auditing purposes.*

As noted above, should such examples be of full face, one-side of face, or magnified close-up photographs? Will the Agency include photographic examples in the Guidance document rather than each company generating their own set of examples for investigators? Does the Agency have a preferred media for these photographs (printed on paper vs. electronic)? Does the Agency recommend the IGA assessment be made from visualizing the patient in the office setting without any reference to the photograph taken at assessment time point?

- On page 14 (Line 396-Line 397), the Guidance states

*When counting facial acne lesions, it is important that all lesions be counted, including those present on the nose.*

The problem in counting the lesions on the nose is that many acne patients have a large number of lesions due to *trichostasis spinulosa* in this particular anatomical area, that resemble open comedones but which are highly resistant to pharmacological therapy. While it may be relevant to count inflammatory lesions on the nose, including this area for counts of non-inflammatory lesions will inappropriately mask treatment-induced improvements in this endpoint in other parts of the face.

## **Outcomes Research**

- On page 10 (Line 406-Line 409), the Guidance states:

*The Agency is interested in patient-reported outcome information; however, such information should not be used as a substitute for objective data or as a surrogate for efficacy. For patient-reported outcome assessments, objective measures could be helpful tools, which may inform both the patient and clinician.*

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The statement in bold is somewhat confusing and needs further clarification. Typically, patient-reported outcome assessments are subjective measures so it is not clear what is meant by the use of objective tools for these outcomes. Can the Agency please clarify what is meant by the bolded statement?

If there are any questions or comments regarding this submission, please contact me at 734/622-1981, or send a fax to 734/622-2856.

Sincerely,

A handwritten signature in black ink, appearing to read "LaVonne L. Lang for".

LaVonne L. Lang, DrPH

Director

Worldwide Regulatory Strategy

Pfizer Inc

LLL/nb